PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN0397-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NO2004/000393	International filing date *(day/month/year)* 17.12.2004	Priority date *(day/month/year)* 18.12.2003
International Patent Classification (IPC) or national classification and IPC A61K49/00		
Applicant AMERSHAM HEALTH AS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.10.2005	09.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Veronese, A Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000393

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-29 as originally filed

   Claims, Numbers

   1-13 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10-13 (IA)

because:

☒ the said international application, or the said claims Nos. 10-13 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 10-13 (IA)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000393

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4
	No:	Claims	1-3,5-13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

Claims 10-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(1) PCT).

2. Re ItemV.

The following documents have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages indicated in the Search Report:

D1: EP-A-0 800 831 (DAIICHI PURE CHEMICALS CO. LTD) 15 October 1997

D2: WO 00/61194 A (INSTITUT FUER DIAGNOSTIKFORSCHUNG GMBH) 19 October 2000

D3: EP-A-1 170 021 (SHERING AKTIENGESELLSCHAFT) 9 January 2002

D4: WO 01/91805 A (BRACCO RESEARCH USA) 6 December 2001

D5: WO 98/47541 A (NYCOMED IMAGING AS) 29 October 1998

D6: MARCHI-ARTZNER, VALERIE ET AL: "Adhesion of Arg-Gly-Asp (RGD) Peptide Vesicles onto an Integrin Surface: Visualization of the Segregation of RGD Ligands into the Adhesion Plaques by Fluorescence" LANGMUIR , 19(3), 835-841 CODEN: LANGD5; ISSN: 0743-7463, 2003, XP002326372

D7: WO 00/71162 A (MALLINCKRODT INC) 30 November 2000

D8: ACHILEFU S ET AL: "NOVEL RECEPTOR-TARGETED FLUORESCENT CONTRAST AGENTS FOR IN VIVO TUMOR IMAGING" INVESTIGATIVE RADIOLOGY, PHILADELPHIA, PA, US, vol. 35, no. 8, 2000, pages 479-485, XP000978923

D9: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; May 1995 (1995-05), FLÉJOU J F ET AL: "[Overexpression of protein p53 and Barrett esophagus. A frequent and early event in the course of carcinogenesis]" XP002326189 Database accession no. NLM7589998

D10: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; June 1996 (1996-06), CASTELLÀ E ET AL: "Expression of CD44H and CD44v3 in normal oesophagus, Barrett mucosa and oesophageal carcinoma." XP002326190 Database accession no. NLM8763264

D11: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 1999, SEERY J P ET AL: "Abnormal expression of the E-cadherin-catenin complex in dysplastic Barrett's oesophagus." XP002326191 Database accession no. NLM10606424

D12: DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 15 July

1998 (1998-07-15), WILSON K T ET AL: "Increased expression of inducible nitric oxide synthase and cyclooxygenase-2 in Barrett's esophagus and associated adenocarcinomas" XP002326192 Database accession no. EMB-1998243164

D13: WO 2005/002293 A (VANDERBILT UNIVERSITY) 6 January 2005

D14: WO 2005/030266 A (AMERSHAM HEALTH AS) 7 April 2005

D15: WO 01/89584 A (NYCOMED IMAGING AS) 29 November 2001

D16: US-A-5 888 743 (DAS ET AL) 30 March 1999

Novelty (Art.33(2) PCT)

2.1 D1 (EP 0800831) discloses optical imaging contrast agents comprising a conjugate between a vector moiety (preferred are antibodies) and a fluorescent group. Targeting to the p53 protein and use for *in vitro* and *in vivo* targeting of cancer of the oesophagus are disclosed. This document is prejudicial for the novelty of claims 1,3,5, 7-13.

D2 (WO 00161194) and D3 (EP1170021) disclose optical imaging agents comprising a contrast agent made of a fluorescent dye conjugated with a peptide of low molecular weight which is targeted to cancer. The use for imaging of oesophageal cancer is also claimed. D2 also states that the low molecular weight of these conjugates improves the pharmacodynamic properties of the diagnostic agent and decreases the immunogenic responses. In view of this prior art, the subject matter of claims 1-3, 6-13 is not new.

D4 (WO 01/91805) discloses optical imaging agents for the *in-vivo* optical imaging of cancer comprising a vector moiety being a peptide targeted to NP-1 (NP-1 is a type of VEGF receptor), conjugated to a detectable fluorescent moiety. This document does not refer to imaging of oesophagous cancer, however since the VEGF receptor is one of the preferred targets for oesophagous cancer according to the present application (see page 8), the agents disclosed in this document are prejudicial for the novelty of the compound claims 1-3,5-8.

D5 (W09847541) discloses optical imaging agents comprising a vector moiety being an organic moiety or a peptide moiety (one of the preferred vectors being targeted to the VEGF receptor) and a detectable moiety (preferred is a fluorescent moiety). Since the

VEGF receptor is one of the targets for oesophagus cancer according to the description of the present application (page 8), this document is novelty destroying for the compound claims 1-3, 6-8.

D6 (XP002326372) discloses the preparation of conjugates between RGD peptides, which according to the description of the application (see page 10, lines 5-10 and example 4), are suitable to target oesophagous cancer, conjugated to a fluorescence probe. Use for imaging of cancer is disclosed. The compounds disclosed in this document therefore fall in the definition of claims 1-3,6.7.

2.2 Inventive step (Art.33(3) PCT)

The problem underlying the present application is the provision of contrast agents for the optical imaging of Barret's oesophagus and oesophagus cancer. As a solution the inventors propose agents which can be detected by means of optical imaging and which have a preferential affinity for Barret's oesophagus and oesophagus cancer.
Preferred are imaging agents having a molecular weight below 14000 Daltons.
Furthermore, the preferred imaging agents comprise a targeting moiety conjugated to a reporter moiety. A list of reporter moieties is given in claim 5, and others are listed in the description of the application.
As already indicated above, a large part of the subject matter claimed in the present application is not new over the prior art. The subject matter which is not new differs from the prior art in that specific targeting moieties not present in the imaging agents of the prior art have been selected.

D2, D7 and 08 disclose the rational of preparing optical imaging agents made of a fluorescent dye conjugated with a peptide of low molecular weight having affinity for specific tumour types. These documents disclose the advantages of preparing low molecular weight conjugates to improve the pharmacodynamic properties of the contrast agents, to decrease the immunogenic responses and to enhance fluorescence efficiency.

Even if these documents do not specifically mention the imaging of Barret's oesophagus and oesophagus cancer, their teaching indicates that at the date of filing of the present application, the skilled person knew how to prepare optical imaging contrast agents targeted to specific cancer types, how to select the proper reporter moieties, the targeting moieties and how to conjugate them together. For this reason, it appears that, confronted with the problem to prepare imaging agents to image Barret's oesophagus and oesophagus cancer, the skilled person would have selected the targeting moieties listed in claim 5. These are in fact known targeting moieties for Barret's oesophagus and oesophagus cancer (see D9-D12). For this reason, the subject matter underlying the application which is new does not appear to involve an inventive step in the sense of Art.33(3) PCT.

It is also to be observed, that, even if the applicants have provided some explicit examples reporting the synthesis of some preferred imaging agents according to the invention, they have not provided any evidence showing that any of these compounds is suitable to image prostate cancer. It is therefore not clear whether the problem underlying the application has been solved.

2.3 Industrial application (Art.33(4) PCT)

For the assessment of the present claims 10-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Re Item VI

Certain published documents (Rule 70.10)

Application No	Publication date	Filing date	Priority date *(valid claim)*

Patent No	*(day/month/year)*	*(day/month/year)*	*(day/month/year)*
WO 2005/002293	6 January 2005	25 June 2004	25 June 2003
W02005030266	7 April 2005	28-09-2004	29-09-2003

3. Re Item VIII.

Claims 1-4 appear to define the invention as a result to be achieved and to merely claim the underlying technical problem. As such these claims are not considered clear.
Also, some expressions are not clearly defined, rendering unclear the scope of protection of the claimed subject matter, for example: "contrast agent substrate" and "contrast agent product" in claim 4, "fat-related compound" and "traditional organic drug - like small molecules" in claim 6.